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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 07/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/531,438	GIBERT ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-73 and 80-91* is/are pending in the application.

4a) Of the above claim(s) *90 and 91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *42,45-73,81,83,85,87,89* is/are rejected.

7)☐ Claim(s) *42-44,80,82,84,86 and 88* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 42, 60, 72 have been amended.
2. Claims 42-73,80-89 are under consideration.
3. Claims 90-91 stand withdrawn from consideration.
4. Claims 1-41, 74-79 and 92-93 have been canceled.
5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

Objections/Rejections Withdrawn.

6. Claim 72, subparagraph (a) line 3 objected to because of the following informalities: has been obviated through amendment of the claim to recite the term "in" rather than the term "on".

7. Claims 42(subparagraph (b), 44-59,61-73 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, has been obviated in light of the Applicant's traversal and new grounds of rejection set forth below.

8. Claims 42 and 44 rejected under 35 U.S.C. 102(e) as being anticipated by Fach et al et al (US Pat. 5,874,220), in light of Applicant's traversal.

Rejections Maintained

9. Claims 60, 81,83,85,87, 89 rejected under 35 U.S.C. 112, first paragraph, (scope) is maintained for reasons of record in paper number 23, paragraph 13.

10. Claim 60 rejected under 35 U.S.C. 102(b) as being anticipated by Hunter et al (1993) for reasons of record in paper number 23, paragraph 14.

Response to Arguments

11. Applicant's arguments filed April 2, 2004 have been fully considered but they are not persuasive.

12. The rejection of claims 60, 81,83,85,87, 89 [illegible] under 35 U.S.C. 112, first paragraph, is traversed on the grounds that :

a. "the claims clearly stated that the polynucleotides encode a peptide that functions as a secretion signal peptide";

b. "the specification provides extensive guidance with respect to the stringent conditions, microorganisms, SEQ ID NO 4, the requisite elements in an expression vector, construction of vector and the transformation of cells";

c. points to "the specification on page 18, lines 24-31 that provides details for determining whether a peptide functions as a secretion signal peptide" and in the examples on pages 19-22.

13. In response to Applicant's traversal, it is the position of the examiner that the rejection was not a complete absence of enablement , but a scope of enablement rejection.

14. The critical structural components of the secretion signal peptide encoded by SEQ ID NO 4 are not recited in the claims for the nucleic acid that will hybridize to SEQ ID NO 4. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed other than SEQ ID NO 4, and the scope of the claim encompasses variants, fragments and variant

fragments that are not required to comprise the essential lysine charged amino acids at specific locations in the peptide so to define a hydrophobic region and transmembrane domain, thus defining the disclosed species of signal sequence activity.

15. It is well known in the art that hybridization of a nucleic acid to a reference sequence can hybridize to the reference sequence and encode a different amino acid sequence from that of the reference sequence. The instant specification teaches that amino acids within the ranges of 6-26 of SEQ ID NO 4 are critical to the claimed peptide signal sequence activity; the claimed nucleic acid that hybridizes to SEQ ID NO 4 is not required to encode a peptide that comprises the claimed critical range of amino acids that the instant specification defines as essential to the recited biological activity.

16. Since SEQ ID NO 4 is a coding sequence, a nucleic acid that hybridizes to SEQ ID NO 4, could be anti-sense DNA and not encode a secretion signal peptide.

17. Applicant traverses the scope of enablement rejection through citing SEQ ID NO 4, and the disclosure used to describe this species of invention. The examiner did not state that Applicant was not enabled for SEQ ID NO 4, but directed the scope of enablement to the embodiment of the claimed invention that is directed to a genus of nucleic acids that will hybridize to any portion or region of SEQ ID NO 4 and can be of any size, as long as the encoded peptide evidences the recited secretion signal activity. The scope of enablement rejection is maintained for reasons of record in paper number 23 in light of the critical combination of structural components are not required for the nucleic acids that will hybridize to SEQ ID NO 4.

18. The rejection of claim 60, 81,83,85,87,89 under 35 U.S.C. 102(b) as being anticipated by Hunter et al (1993) is traversed on the grounds that "the nucleotide sequence of Hunter and SEQ ID NO 4 do not have a high degree of structural homology" and "share approximately 33% identity".

19. It is the position of the examiner that the claimed invention is directed to:

" A purified nucleic acid comprising" "a sequence from a Clostridium strain which hybridizes under stringent conditions to SEQ ID NO 4".

Reference sequence SEQ ID NO 4:----------

The claimed nucleic acid :XXXXXXXXXXXXXXXXXXX---------XXXXXXXXXXX

The claimed nucleic acid need not hybridize over the full length of SEQ ID NO 4, but must only comprise a sequence that would hybridize to SEQ ID NO 4. The sequence alignment provided by Applicant that shows 33% sequence identity between SEQ ID NO 4 of the instant Application and the sequence of Hunter et al, provides evidence that the sequence of Hunter does comprise a sequence which would hybridize to the compliment of SEQ ID NO 4, specifically "ATGAGAAAA" which evidences only one difference over a region of 10 nucleotides of SEQ ID NO 4, (90% sequence identity). The claimed purified nucleic acid must comprise this sequence, must encode a peptide that functions as a secretion signal peptide and be from a Clostridial strain; all of these elements are true of the purified nucleic acid disclosed by Hunter et al.

Clearly that purified nucleic acid of Hunter et al encodes a signal secretion sequence, comprises a nucleic acid sequence that would hybridize to SEQ ID NO 4, and is a Clostridium perfringens nucleic acid . The nucleic acid that must hybridize to SEQ Id NO 4, is not required

to be any number of consecutive nucleic acids of SEQ ID NO 4, to be of any specific size, or comprise any conserved sequence of nucleotides to encode any specific conserved amino acid sequence, but must only comprise a sequence that would hybridize, therefore To a fragment of the disclosed purified nucleic acid of Hunter et al would hybridize to SEQ ID No 4, is purified, is from a Clostridial strain, and encodes a signal secretion amino acid sequence.

The claims do not require the claimed purified nucleic acid to hybridize over the full length of SEQ ID NO 4, to evidence any specific degree of homology, identity or similarity to SEQ Id NO 4, but must only comprise a sequence of nucleotides that would hybridize to SEQ ID NO 4.

Applicant compares a nucleotide sequence of 90 consecutive nucleic acids of Hunter to the full sequence of SEQ ID NO 4, but this specific embodiment is not what is currently claimed. Hunter et al still anticipates the instantly claimed invention, because Applicant's arguments are not commensurate in scope with the instantly claimed invention.

Election/Restrictions

20. Applicant's traverse the election by original presentation of claims 90-91 on the ground(s) that " The Examiner's attention is directed to a similar claim, Claim 73, which is also directed to a method of producing a polypeptide". This is not found persuasive because claims 90-91 are not directed to a method of producing the polypeptide of claim 73, but to making a different polypeptide not previously examined. Upon agreement of allowable subject matter, a method of making or a method of using may be rejoined of the exact scope of the allowable subject matter (see Ochiai/Brouwer paragraph below).

Ochiai/Brouwer Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of

the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Allowable Subject Matter

21. Claims 43, 44 and 42, subparagraph (a), 60 SEQ ID NO 4, and claims 80,82,84,86 and 88 (paragraph a) comprise subject matter that defines over the prior art of record (see paragraphs 7-10, paper number 23) but are objected to as reciting a rejected embodiment or dependent upon a rejected base claim, but would be allowable upon obviation of the objection.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

22. Claim 42(b) and claims 50-51, 54-55 (b) are rejected under 35 U.S.C. 102(b) as being anticipated by Graves et al (1986).

(Instant claim 42, subparagraph (b)) Graves et al disclose the instantly claimed invention directed to a purified nucleic acid that comprises a nucleic acid sequence "aaaaa" (see Figure 7, line 20 of a Clostridial strain) and an additional sequence, "tttaaa" (see Figure 5, designated "P1" line A-B, page 1412; positions 35-40 of instant SEQ ID NO 4) and "ttttaaaaa" (see Figure 5, designated "P1", line C-D, positions 148-156 of instant SEQ ID NO 4) these sequence fragments being able to hybridize to the complementary strand of SEQ ID No 3 under stringent conditions, wherein the purified nucleic acid has a transcriptional promoter activity (see title) and is from a Clostridial strain, specifically Clostridium pasteurian .

(Instant claims 50-51, 54-55, all dependent from Instant claim 42, subparagraph (b))

The Clostridium pasteurian promoter was cloned into a plasmid vector which was then subcloned into a functional bacteria (E.coli) (see page 11410, col. 1, paragraphs 3-5 and col. 2, Figures 1-2; page 11412, entire page and figures). The reference anticipates the instantly claimed purified nucleic acid that evidences transcriptional promoter activity, and comprises a sequence from a Clostridium strain that will hybridize to SEQ ID NO 3.

23. Claim 42(paragraph b) and claims 45-73,81,83,85,87,89 (paragraph b) are rejected under 35 U.S.C. 102(b) as being anticipated Brown (1997; Dissertation abstract international).

(Instant claim 42, subparagraph (b)) Brown disclose the instantly claimed invention directed to a purified nucleic acid that comprises a nucleic acid sequence that evidences Clostridial promoter elements for transcription (see paragraph 5), where in the Clostridial transcriptional promoter is a Clostridium perfringens promoter element (see paragraph 5).

The purified transcriptional promoter was incorporated within an expression cassette (vector) to control the production of recombinant fragments of a transgene, the transgene encoding fragments of "BoNT/A" (botulinum toxin A (see meaning of term in paragraph 3, lines 1-2). The transcriptional promoter/transgene coding sequences were associated with a secretory leader sequence that encoded for a peptide that would direct section of the recombinant protein outside the recombinant host cell that comprised the expression vector. The recombinant expression of the transgene product was successfully expressed in C. perfringens strain 13 (see paragraph 5).

The purified nucleic acids inherently comprise at least a portion of SEQ ID NO 3 and 4, the portions being nucleic acid sequences that would hybridize to the reference sequences of SEQ Id NO 4 and the purified nucleic acids comprising these portions.

The reference inherently anticipates the instantly claimed purified nucleic acid that evidences transcriptional promoter activity, encodes a transgene product and a secretion signal sequence of a Clostridial strain, specifically Clostridium perfringens.

Conclusion

24. This is a non-final office action.

25. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

26. US Patents (6,403,094; 6,323,023; 6,280,993; 6,713,617; 5955368; 5496725; 5418157; 5177017) are cited to show Clostridium promoters and/or cloning systems.
27. Bullifent et al (1995) is cited to show a reporter system for Clostridium perfringens gene expression that comprises a promoter region of the alpha toxin gene of C. perfringens (see abstract).
28. Garnier, T et al (1988 and 1991) is cited to show replication functions of a plasmid from Clostridium perfringens.
29. Holck, A et al (1990) is cited to show genes for Clostridium perfringens spore proteins.
30. Hunter et al (1992) is cited to show a 5' sequence with conserved consensus nucleotides that are apart of a signal/promoter sequence (see page 105, col. 2, paragraph 2) and page 106, Figure 5, and narrative for figure).
31. Kobayashi, T et al (1995) is cited to show transcriptional analysis of a Clostridium perfringens gene.
32. Lyristis, M et al (1994) is cited to show a locus that regulates extra cellular toxin production in Clostridium perfringens.
33. Narberhaus et al (1992) is cited to show TTGCTA to be a promoter structure for Clostridium acetobutylicum.
34. Saint-Joanis, B et al, Molecular and general genetics (1989) is cited to show the gene for Clostridium perfringens alpha toxin.
35. Sauer et al (1994) is cited to show a promoter sequence from Clostridium acetobutylicum (see abstract, and entire document).

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
June 22, 2004

L. F. Smith

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